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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/974,592	10/09/2001	Robert G. Korncluk	07891/009004	8174

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EXAMINER	
HUDSON, AMY J	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/974,592	KORNELUK ET AL.	
	Examiner	Art Unit	
	Amy J Hudson	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *1-4 and 6-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5 and 9-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Claims 1-4 and 6-8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 9/3/2002.

Response to Amendment

Upon filing Request for Continued Examination, the amendment received 12/11/03 has been entered and considered in this evaluation. See MPEP § 706.07(h), paragraph XI.

Claim Rejections - *35 USC § 112, first paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5 and 9-15 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Response to Arguments

Applicants arguments filed on 6/16/2004 have been fully considered but they are not persuasive to overcome the enablement rejection. Claims 5 and 9-15 remain rejected under 35 U.S.C 112, first paragraph, because the specification, while being enabling for practicing the claimed method *in vitro*, and *in vivo* comprising administering phosphorothioate modified antisense oligonucleotides that are 19 nucleotides in length, does not reasonably provide enablement for the *in vivo* therapeutic treatment of a patient comprising administration of unmodified antisense oligonucleotides of any other length. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, resulting in rejection for the reasons of record as set forth in the official office action mailed on 8/8/2003.

The following quote is taken from the second page of the applicant's remarks filed on 6/16/2004. "The examiner must provide specific technical reasons showing why applicants' disclosure fails to satisfy the enablement requirement." The examiner agrees with this statement. Please refer both to the official office action mailed on 8/8/03, as well as this official office action, for specific technical reasons to support the enablement rejection. Review articles have been cited stating specific, unpredictable factors with the regard to the *in vivo* application of antisense oligonucleotides.

Evidence is required to support an enablement rejection

While the applicant argues that XIAP oligonucleotides may be used to induce apoptosis in a cell regardless of the length of the antisense oligonucleotide, this is not consistent with the breadth of the claims. As stated in the previous office action (final rejection), the instant claims merely state that the antisense oligonucleotides used in the claimed methods are of length sufficient to inhibit and are complementary to a portion of human XIAP. However, applicant's results indicate that mere length and complementarity of the antisense oligonucleotide is not sufficient to result in inhibition of an inhibitor of apoptosis. Specifically, G3 and G4 antisense oligonucleotides are of the same length and are both complementary to XIAP mRNA, however G3 does not down regulate XIAP expression, and the G4 oligonucleotide does inhibit (See Table 1 in Exhibit A).

The Declaration by Korneluk does not demonstrate the effective delivery of antisense oligonucleotides of any length and/or modification, wherein delivery of the antisense nucleic acid results in the treatment of a patient diagnosed with a proliferative disease.

Contrary to applicant's argument with respect to the expectations of apoptosis regardless of the length of the antisense oligonucleotide, these predictions cannot be adequately made without undue experimentation. Evidence to support the unpredictability of the *in vivo* behavior of oligonucleotide based compositions is taught by Chirila et al. (2002), Jen et al. (2002), and Stein (2000), as stated in the prior office action (final rejection). Experimentation and instruction regarding this invention is

necessary in the specification in order to meet the enablement requirements. Specifically, each distinct antisense must be tested individually for delivery, the ability to enter the correct target cells, toxicity profiles, etc. Braasch and Corey (2002) discuss the difficulty in identifying oligonucleotides that act as potent inhibitors of gene expression, due to many factors including difficulties predicting the secondary structures of RNA and the occurrence of non-intended interactions. These are additional reasons why individual testing is needed for each antisense oligonucleotide. Branch (1998) states that since a single, well-understood mechanism of action cannot be assumed; difficulties remain in determining which exact antisense oligonucleotides will prove to be effective.

Routine screening identifies antisense oligonucleotides

Applicant argues that the skilled artisan can routinely and easily screen any antisense oligonucleotide, regardless of length, for its ability to induce apoptosis in a cell. Although screening is a common technique in the field, this does not enable the necessity for one skilled in the art to predict the outcome of those antisense oligonucleotides to human X-linked IAP that would function *in vivo* without further experimentation. Simply being able to screen cells *in vitro* is not sufficient to enable this specific antisense oligonucleotide, *in vivo.* Although applicant explains the general antisense mechanism of all antisense oligonucleotides in their argument (Lacasse Declaration), the issue remains regarding the unpredictability of how the antisense over the breadth claimed will perform *in vivo*. Understanding the general antisense

mechanism *in vitro* does not enable this antisense oligonucleotide for predictable use in treating a patient that has been diagnosed with a proliferative disease.

Antisense oligonucleotide length is not a determinant of efficacy

By referring to prior art, applicant has shown that there are antisense oligonucleotides of various lengths that do work *in vivo*, but has not demonstrated this for the claimed antisense oligonucleotide. The examples set forth by the applicant do not display a correlation to the gene of issue. Secondly, nor does the specification offer specific guidance of how the invention is to be reproduced and predictable in an appropriate model. The previous art cited by the applicant does not overcome the unpredictability of the outcome at this time.

Applicant cites Shankar, Kallio and Fukada as references to enable the usage of various lengths of antisense oligonucleotides effectively. Although it is shown that various lengths of oligonucleotides have been used to down regulate genes, no evidence has been shown that this correlates with the inhibition of human X-linked IAP. Each antisense oligonucleotide must be tested de novo. The specification does not offer the necessary guidance (experimentation and explanation) to enable an antisense oligonucleotide of "length sufficient to inhibit an inhibitor of apoptosis (IAP)." Applicant argues that there is no reason to expect that a XIAP antisense oligonucleotide that is nineteen nucleotides in length is unique in its ability to induce apoptosis. On the contrary, it is well recognized in the field that de novo testing is needed for each

antisense oligonucleotide. Drawing assumptions alone is not adequate to overcome the enablement requirement.

As stated by Tamm et al, "proof of clinical efficacy, of any of the antisense oligonucleotides in the field of oncology, is still missing". Tamm et al. explain that only if the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence will there be some extent of predictability. At the time of application, the art was known to be unpredictable. Therefore, applicant must overcome the unpredictability of the art by giving detailed guidance on how the invention is to work and treat a patient diagnosed as having a proliferative disease. Based on the unpredictability of the antisense mechanism, it cannot be assumed that the antisense oligonucleotide claimed will routinely produce the desired result as claimed. It is known in the field that both antisense effects *in vivo*, as well as the functionality (apoptosis) are unpredictable at the time the invention was applied for. Specific guidance has not been given by the applicant to overcome the unpredictability of the *in vivo* response.

Conclusion

Applicant concludes that abundant evidence has been provided showing that virtually any antisense oligonucleotide that binds to its complementary target mRNA will inhibit protein production. This statement is contrary to the language of claim 5, which draws on a method of inducing apoptosis. The inhibition of protein production and

apoptosis are distinct events, which require much different dosages. Therefore, it is unclear what the point is of the concluding sentence of the applicant remarks.

Based on evidence as a whole, the rejection of claims 5 and 9-15 is maintained. The specification does not describe the use and full scope of antisense oligonucleotides encompassed by the instant claims as an inhibitor of human X-linked IAP for the *in vivo* treatment of a disease in a sufficient manner so as to enable one of ordinary skill in the art to practice the full scope of the present invention without undue experimentation and with a predictable result. This conclusion is based on the known unpredictability of the delivery of antisense oligonucleotides *in vivo* (as well as the unpredictability of the behavior and functionality of the antisense oligonucleotide once in a cell), the breadth of the claims, and the lack of guidance presented in the specification regarding the successful *in vivo* usage of the invention. With regards to the unpredictable nature of the functionality, the inhibition of the target gene itself is even unpredictable. These rejections are supported by the art cited in this official office action, as well as the art cited in the previous official office action (8/8/2003). Findings regarding one antisense oligonucleotide cannot necessarily be applied to another antisense oligonucleotide. Each must be tested individually in order to determine its effective response. Sufficient guidance has not been given in the specification to overcome the unpredictability of the mechanism and outcome. Therefore, undue experimentation would be needed in order to practice this invention.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is not clear in view of the language "in a mammal diagnosed as having a proliferative disease." There does not appear to be a connection between the preamble and the body of the claim. There is no apparent relationship (cause/effect or otherwise) between "A method of inducing apoptosis in a cell" and "in a mammal diagnosed as having a proliferative disease." There is no connective relationship between the method and a mammal diagnosed with a proliferative disease to demonstrate which cells are of interest. It is unclear what the claimed effect is on the claimed method by the mammal.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy Hudson whose telephone number is 571-272-0755. The examiner can normally be reached on Mon-Fri 7:30 am – 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance.

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